The paragraphs presented above incorporate changes as indicated by the marked-up versions below.

Page 18, line 6:

In preferred embodiments, R5 is a hydrogen, or a ~~halogentated~~ halogenated lower alkyl.

Page 18, line 9:

In preferred embodiments, R_{61} and R_{62}, independently, represent lower alkyls, such as methyl, ethyl, propyl, isopropyl, tert-butyl or the ~~lik.~~ like;

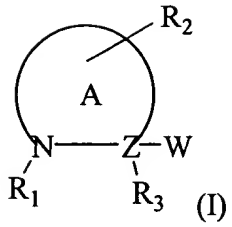
The present invention provides methods and compositions for modification and regulation of GLP 1 metabolism, glucose and lipid metabolism, generally to reduce insulin resistance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoprotein-emia (such as chylomicrons, VLDL and LDL), and to regulate body fat and more generally lipid stores, and, more generally, for the improvement of metabolism disorders, especially those associated with diabetes, obesity and/or atherosclerosis. The compositions described herein are high-affinity boronyl and non-boronyl peptidomimetic inhibitors of DPIV.

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below. Please cancel claim 15 without prejudice.

Q4

1. (Amended) A method for modifying, in an animal, metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to the animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1, wherein the inhibitor is represented by Formula I:



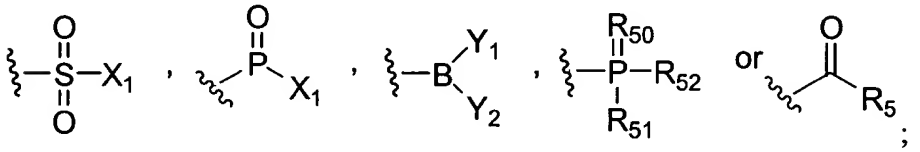
(I)

wherein

A represents a 4-8 membered heterocycle including the N and a Cα carbon;

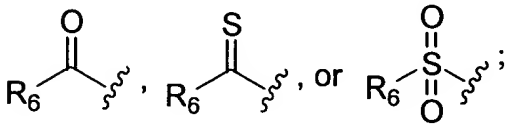
Z represents C or N;

W represents -CH=NR5, a functional group which reacts with an active site residue of the targeted protease, or



;

R1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



;

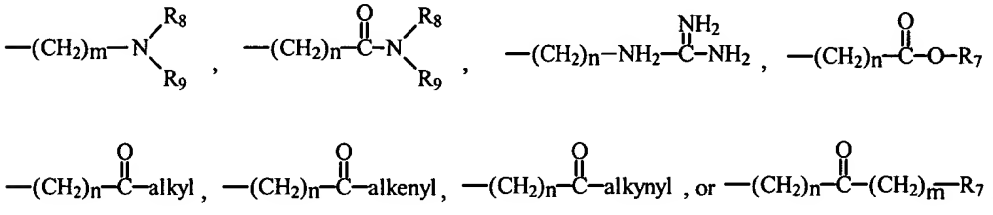
R2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

if Z is N, R3 represents hydrogen, if Z is C, R3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-$

R_7, $-(CH_2)_m$-SH, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, or $-(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m$-R_7, $-(CH_2)_n$-OH, $-(CH_2)_n$-O-alkyl, $-(CH_2)_n$-O-alkenyl, $-(CH_2)_n$-O-alkynyl, $-(CH_2)_n$-O-$(CH_2)_m$-R_7, $-(CH_2)_n$-SH, $-(CH_2)_n$-S-alkyl, $-(CH_2)_n$-S-alkenyl, $-(CH_2)_n$-S-alkynyl, $-(CH_2)_n$-S-$(CH_2)_m$-R_7, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m$-R_7, $-(CH_2)_m$-OH, $-(CH_2)_m$-O-alkyl, $-(CH_2)_m$-O-alkenyl, $-(CH_2)_m$-O-alkynyl, $-(CH_2)_m$-O-$(CH_2)_m$-R_7, $-(CH_2)_m$-SH, $-(CH_2)_m$-S-alkyl, $-(CH_2)_m$-S-alkenyl, $-(CH_2)_m$-S-alkynyl, or $-(CH_2)_m$-S-$(CH_2)_m$-R_7,



;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or $-C(=O)-(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

2. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit DPIV-mediated proteolysis, wherein the inhibitor is represented by Formula I.

3. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) and accordingly increase the plasma half-life of GLP-1, wherein the inhibitor is represented by Formula I.

4. (Amended) A method for treating Type II diabetes, comprising administering to an animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV) represented by Formula I.

5. (Amended) The method of claim 1, wherein the dipeptidylpeptidase is DPIV.

6. (Amended) The method of claim 3, wherein the protease inhibitor is an inhibitor of DPIV.

7. (Amended) The method of claim 2 or 3, wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

8. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

9. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for inhibition of glucose intolerance in the nanomolar or less range

10. (Amended) The method of claim 8, wherein the inhibitor has an EC_{50} for immunosuppression in the μM or greater range.

11. (Amended) The method of claim 4, 5 or 6, wherein the inhibitor has a Ki for DPIV inhibition of 1.0 nM or less.

A4 Conclude

12. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor is peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

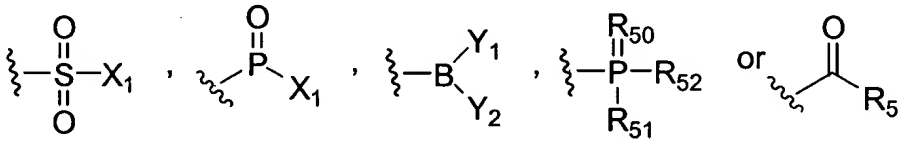
13. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has a molecular weight less than 7500 amu.

14. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor is administered orally.

A5

16. (Amended) The method of claim 1, 2, 3, or 4, wherein

W represents $-CH=NR_5$,



R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)m-R_7$, $-(CH_2)n-OH$, $-(CH_2)n-O-alkyl$, $-(CH_2)n-O-alkenyl$, $-(CH_2)n-O-alkynyl$, $-(CH_2)n-O-(CH_2)m-R_7$, $-(CH_2)n-SH$, $-(CH_2)n-S-alkyl$, $-(CH_2)n-S-alkenyl$, $-(CH_2)n-S-alkynyl$, $-(CH_2)n-S-(CH_2)m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; Y_1 and Y_2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including

cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

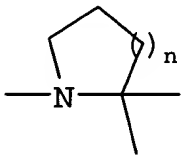
X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

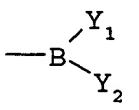
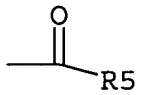
m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

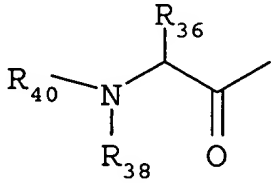
17. (Amended) The method of claim 16, wherein the ring A is represented by the formula:



wherein n is an integer of 1 or 2.

18. The method of claim 16, wherein W represents  or  .

19. The method of claim 16, wherein R_1 represents



R_{36} is a small hydrophobic group and R_{38} is hydrogen, or, R_{36} and R_{38} together form a 4-7 membered heterocycle including the N and the Cα carbon, as defined for A above; and

R_{40} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

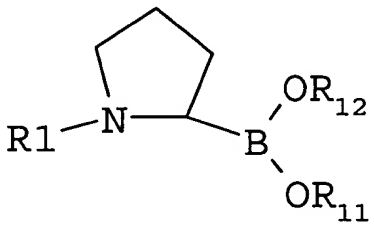
20. (Amended) The method of claim 16, wherein R_2 is absent, or represents a small hydrophobic group.

21. (Amended) The method of claim 16, wherein R_3 is a hydrogen, or a small hydrophobic group.

22. (Amended) The method of claim 16, wherein R_5 is a hydrogen, or a halogenated lower alkyl.

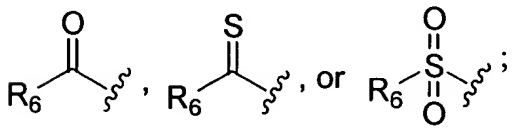
23. (Amended) The method of claim 16, wherein X_1 is a fluorine, and X_2 and X_3, if halogens, are fluorine.

24. (Amended) The method of claim 16, wherein the inhibitor is represented by the general formula:

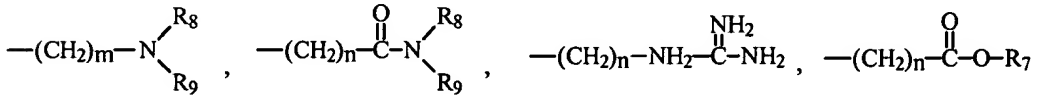


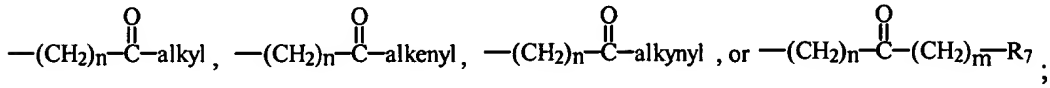
wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,





;

R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

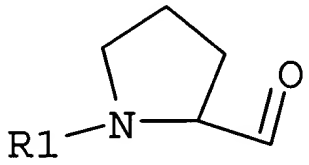
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{11} and R_{12} each independently represent hydrogen, a alkyl, or a pharmaceutically acceptable salt, or R_{11} and R_{12} taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

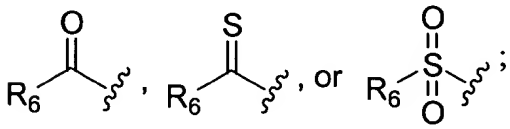
m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

25. (Amended) The method of claim 16, wherein the inhibitor is represented by the general formula



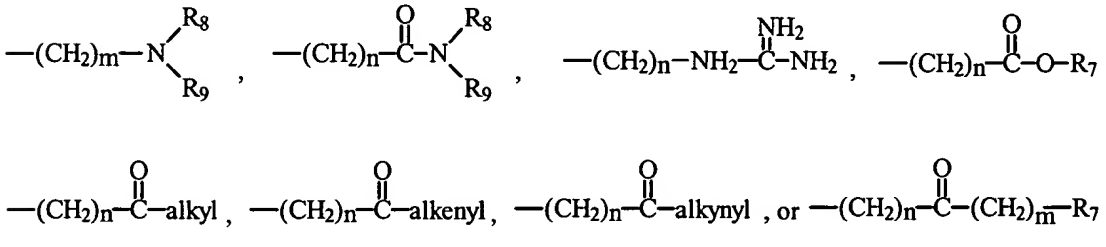
wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



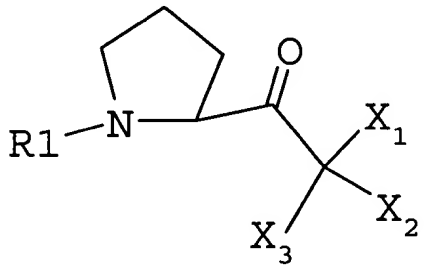
R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

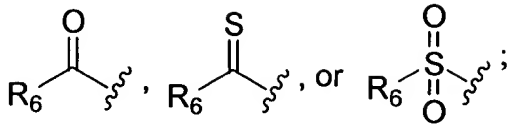
m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

26. (Amended) The method of claim 16, wherein the inhibitor is represented by the general formula:

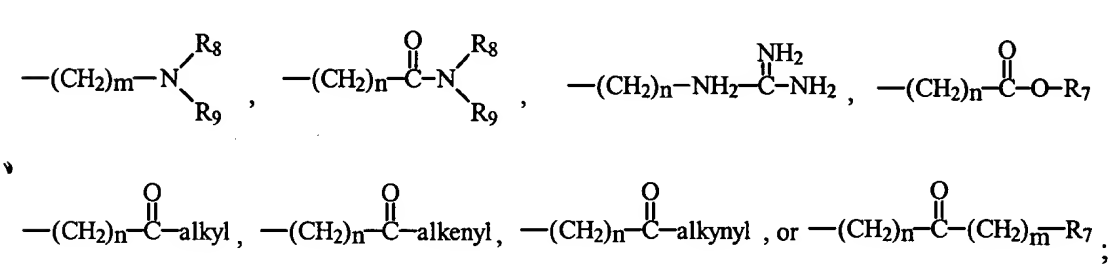


wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

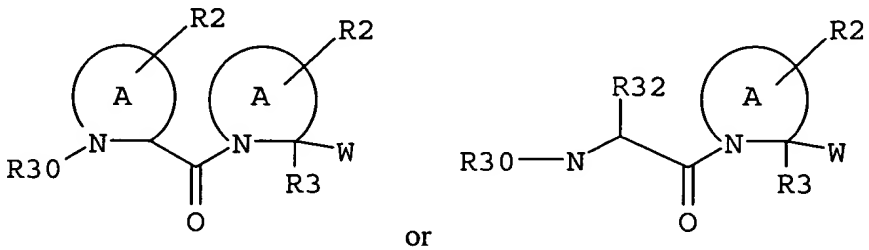
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

X_1, X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

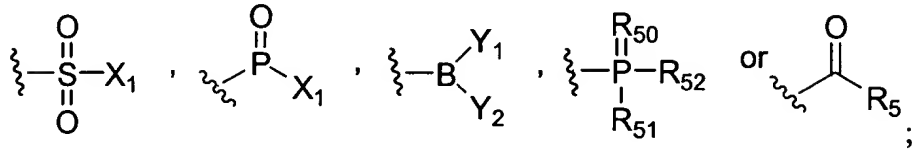
27. (Amended) The method of claim 16, wherein the inhibitor is represented by the general formula:



or

wherein
A represent a 4-8 membered heterocycle including an N and a Cα carbon;

W represents, -CH=NR_5,



R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

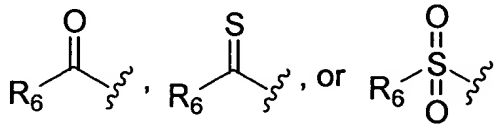
R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n$-O-alkyl, $-(CH_2)_n$-O-alkenyl, $-(CH_2)_n$-O-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n$-S-alkyl, $-(CH_2)_n$-S-alkenyl, $-(CH_2)_n$-S-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_{32} is a small hydrophobic group;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, or



R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

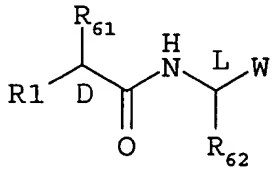
X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

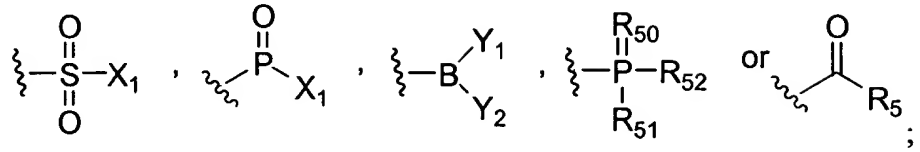
28. (Amended) A method for modifying, in an animal, metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to the animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1,, wherein the inhibitor is represented by Formula II:



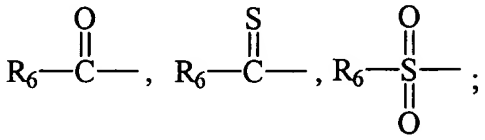
(II)

wherein

W represents a functional group which reacts with an active site residue of the targeted protease, selected from -CN, -CH=NR_5,



R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)m-R_7$, $-(CH_2)n-OH$, $-(CH_2)n-O$-alkyl, $-(CH_2)n-O$-alkenyl, $-(CH_2)n-O$-alkynyl, $-(CH_2)n-O-(CH_2)m-R_7$, $-(CH_2)n-SH$, $-(CH_2)n-S$-alkyl, $-(CH_2)n-S$-alkenyl, $-(CH_2)n-S$-alkynyl, $-(CH_2)n-S-(CH_2)m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl, or $-(CH_2)_m-S-(CH_2)_m-R_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{61} and R_{62}, independently, represent small hydrophobic groups;

Y_1 and Y_2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'$_7$;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'$_7$, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure

X_1 represents a halogen;

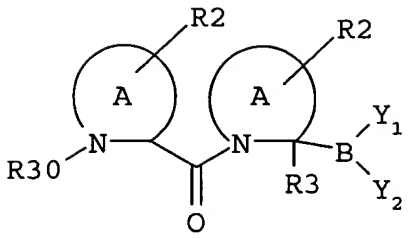
X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

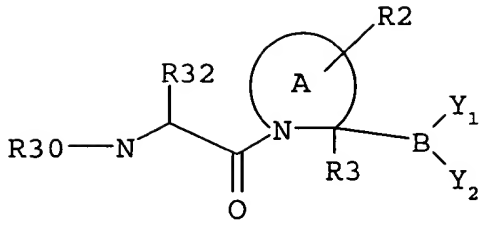
29. (Amended) A method for modifiying, in an animal, metabolism of peptide hormone, comprising administering to the animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV) in an amount sufficient to increase the plasma half-life of a peptide hormone, which peptide hormone is selected from glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

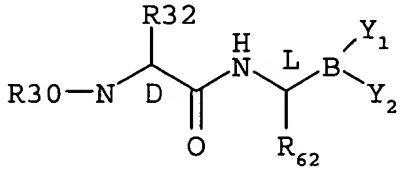
30. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including boronyl peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

31. (Amended) The method of claim 31, wherein the boronyl peptidomimetic is represented in the general formula:



or





or

wherein

each A independently represents a 4-8 membered heterocycle including the N and a Cα carbon;

R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

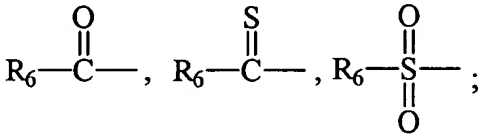
R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, -(CH2)m-R7, -(CH2)n-OH, -(CH2)n-O-alkyl, -(CH2)n-O-alkenyl, -(CH2)n-O-alkynyl, -(CH2)n-O-(CH2)m-R7, -(CH2)n-SH, -(CH2)n-S-alkyl, -(CH2)n-S-alkenyl, -(CH2)n-S-alkynyl, -(CH2)n-S-(CH2)m-R7, $-C(O)C(O)NH_2$, or -C(O)C(O)OR'7;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m$-O-alkyl, $-(CH_2)_m$-O-alkenyl, $-(CH_2)_m$-O-alkynyl, $-(CH_2)_m$-O-

$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, or -$(CH_2)_m$-S-$(CH_2)_m$-R_7;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



R_{32} and R_{61}, independently, represent small hydrophobic groups;

Y_1 and Y_2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

32. (Amended) The method of claim 31, wherein administering the boronyl peptidomimetic reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia.

33. (Amended) The method of claim 31, wherein the boronyl peptidomimetic has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

34. (Amended) The method of claim 31, wherein the boronyl peptidomimetic has an EC_{50} for inhibition of glucose tolerance in the nanomolar or less range.

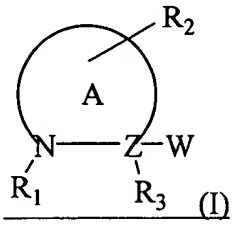
35. (Amended) The method of claim 31, wherein the boronyl peptidomimetic has an EC_{50} for immunosuppression in the μM or greater range.

36. (Amended) The method of claim 31, wherein the boronyl peptidomimetic is administered orally.

37. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition comprising a peptidomimetic boronyl inhibitor wherein the peptide to be mimicked is Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. (Amended) A method for modifying, in an animal, metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to the animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1, ~~which inhibitor(s) are administered in an amount sufficient to inhibit the dipeptidylpeptidase proteolysis of GLP-1~~wherein the inhibitor is represented by Formula I:



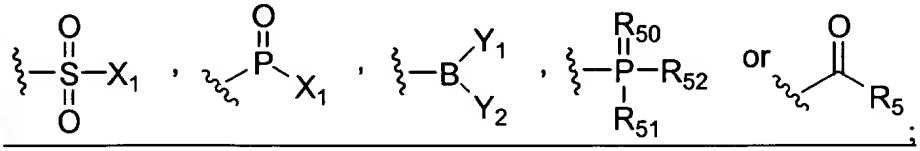
(I)

wherein

A represents a 4-8 membered heterocycle including the N and a Cα carbon;

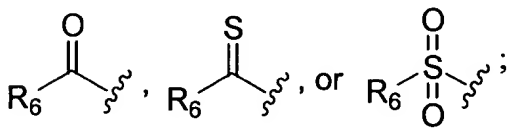
Z represents C or N;

W represents -CH=NR5, a functional group which reacts with an active site residue of the targeted protease, or



;

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



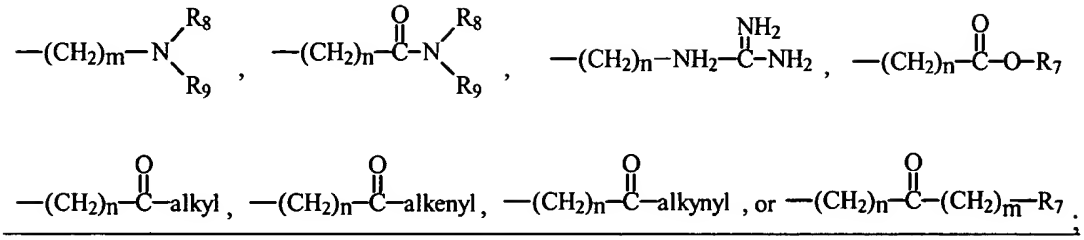
R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

if Z is N, R_3 represents hydrogen, if Z is C, R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl,

or -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

2. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit DPIV-mediated proteolysis ~~with a Ki of 1nM or less.~~, wherein the inhibitor is represented by Formula I.

3. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) and accordingly increase the plasma half-life of GLP-1, wherein the inhibitor is represented by Formula I.

4. (Amended) A method for treating Type II diabetes, comprising administering to an animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV) represented by Formula I.

5. (Amended) The method of claim 1, wherein the dipeptidylpeptidase is DPIV.

6. (Amended) The method of claim 3, wherein the protease inhibitor is an inhibitor of DPIV.

7. (Amended) The method of claim 2 or 3, wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

8. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

9. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for inhibition of glucose intolerance in the nanomolar or less range

10. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for immunosuppression in the μM or greater range.

11. (Amended) The method of claim 4, 5 or 6, wherein the inhibitor has a Ki for DPIV inhibition of 1.0 ~~nm~~ nM or less.

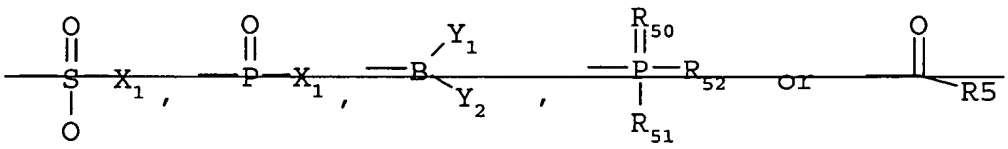
12. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor is peptidomimetic of a peptide selected from ~~the group consisting~~ Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

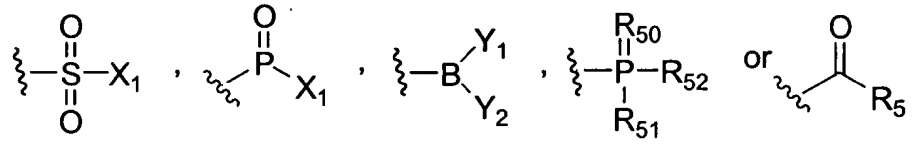
13. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has a molecular weights less than 7500 amu.

14. (Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor is ~~orally active~~administered orally.

16. (Amended) The method of claim ~~15~~1, 2, 3, or 4, wherein

W represents ~~-CN,~~ -CH=NR5,





R5 represents H, an alkyl, an alkenyl, an alkynyl, -C(X1)(X2)X3, -(CH2)m-R7, -(CH2)n-OH, -(CH2)n-O-alkyl, -(CH2)n-O-alkenyl, -(CH2)n-O-alkynyl, -(CH2)n-O-(CH2)m-R7, -(CH2)n-SH, -(CH2)n-S-alkyl, -(CH2)n-S-alkenyl, -(CH2)n-S-alkynyl, -(CH2)n-S-(CH2)m-R7, -C(O)C(O)NH2, or -C(O)C(O)OR'7;

R7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; ~~and~~

Y1 and Y2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where Y1 and Y2 are connected via a ring having from 5 to 8 atoms in the ring structure ~~(such as pinacol or the like),;~~

R50 represents O or S;

R_{51} represents N_3, SH_2, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

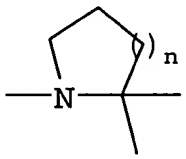
X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

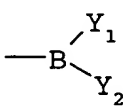
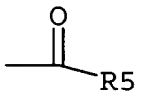
m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

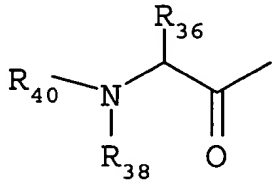
~~18~~17. (Amended) The method of claim 16, wherein the ring A is represented by the formula:



wherein n is an integer of 1 or 2.

~~19~~18. The method of claim 16, wherein W represents  or  .

~~20~~19. The method of claim 16, wherein R_1 represents



~~wherein~~

R_{36} is a small hydrophobic group and R_{38} is hydrogen, or, R_{36} and R_{38} together form a 4-7 membered heterocycle including the N and the Cα carbon, as defined for A above; and

R_{40} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

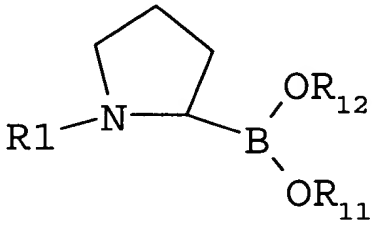
~~21~~20. (Amended) The method of claim 16, wherein R_2 is absent, or represents a small hydrophobic group.

~~22~~21. (Amended) The method of claim 16, wherein R_3 is a hydrogen, or a small hydrophobic group.

~~23~~22. (Amended) The method of claim 16, wherein R_5 is a hydrogen, or a ~~halogentated~~ halogenated lower alkyl.

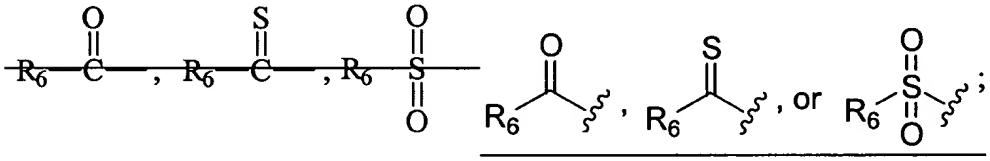
~~24~~23. (Amended) The method of claim 16, wherein X_1 is a fluorine, and X_2 and X_3, if halogens, are fluorine.

~~25~~24. (Amended) The method of claim 16, wherein the inhibitor is represented by the general formula:

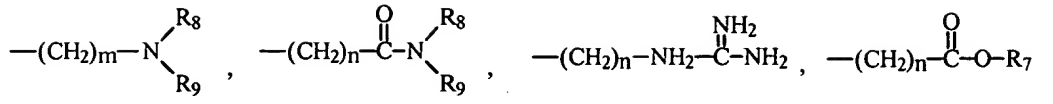


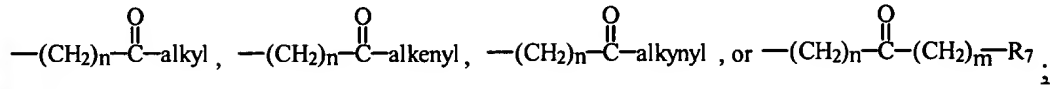
wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,





R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

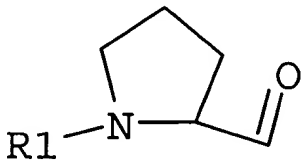
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{11} and R_{12} each independently represent hydrogen, a alkyl, or a pharmaceutically acceptable salt, or R_{11} and R_{12} taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

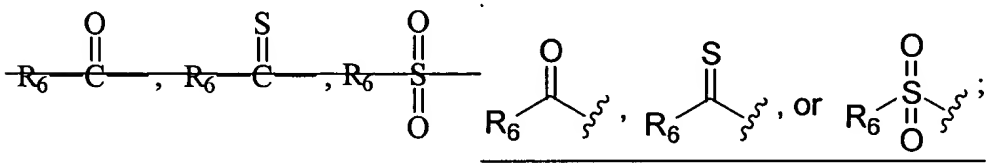
m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

~~26~~25. (Amended) The method of claim 16-, wherein the inhibitor is represented by the general formula

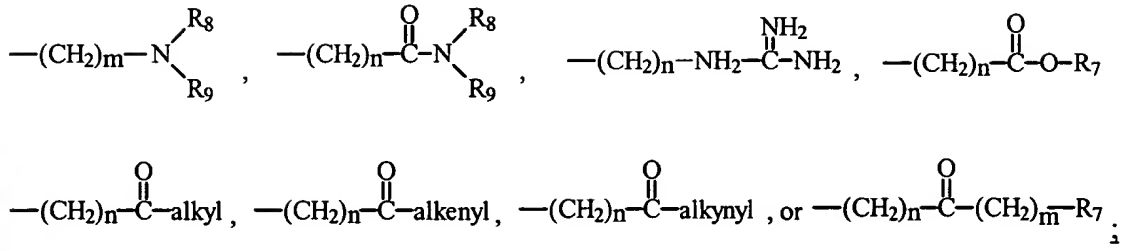


wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



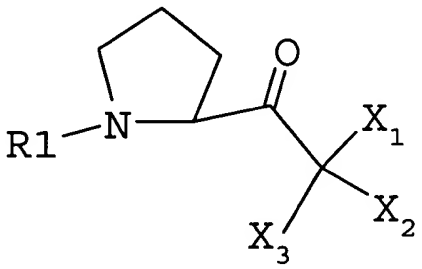
R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure; ~~and~~

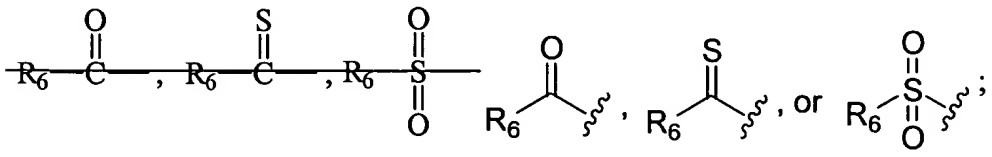
m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

~~27~~26. (Amended) The method of claim 16~~,~~ wherein the inhibitor is represented by the general formula:



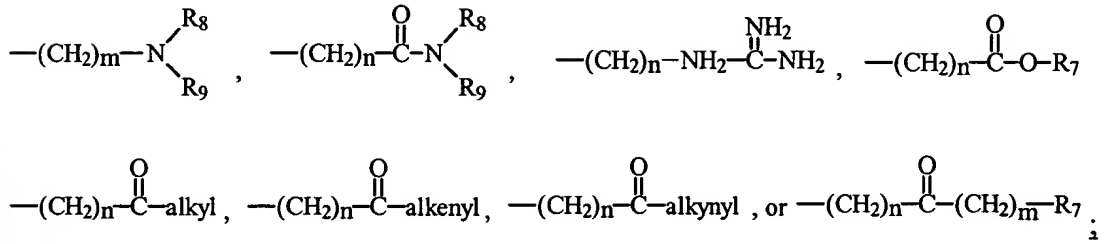
wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-

$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

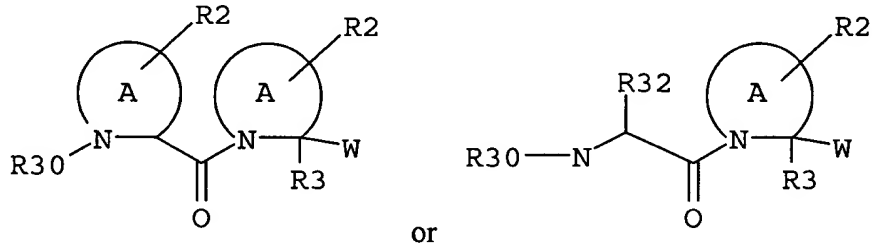
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

X_1, X_2 and X_3 each represent a hydrogen or a halogen; ~~and~~

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

~~28~~27. (Amended) The method of claim 16-, wherein the inhibitor is represented by the general formula:

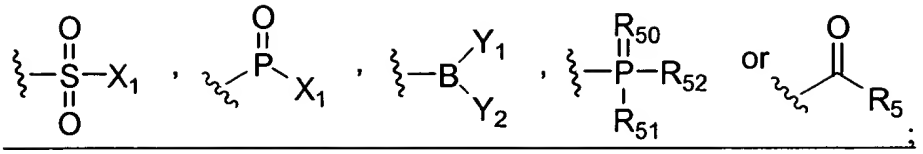


or

wherein

A represent a 4-8 membered heterocycle including an N and a Cα carbon;

W represents, -CH=NR_5,



R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

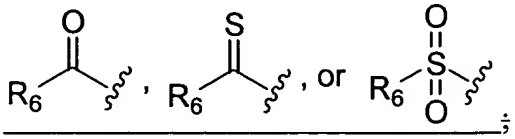
R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_{32} is a small hydrophobic group; ~~and~~

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group. or



R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

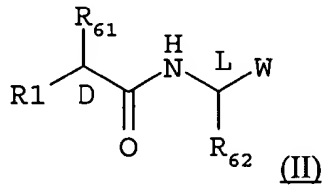
X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

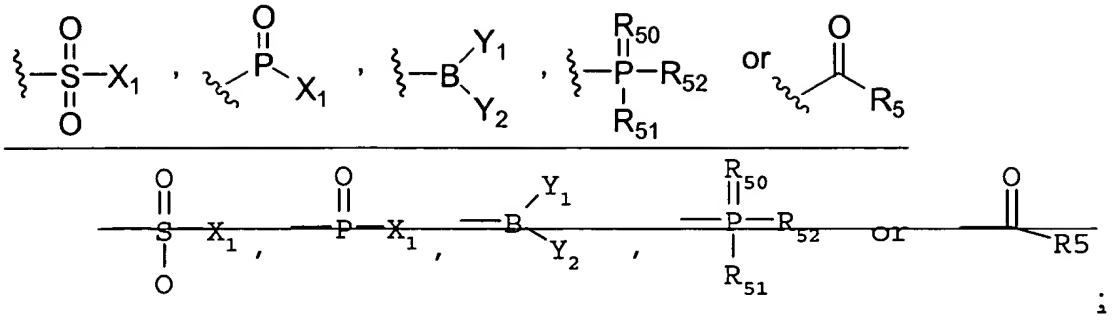
~~29~~28. (Amended) A method for modifying, in an animal, metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to the animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1, ~~The method of claim 16,~~ wherein the inhibitor is represented by ~~the general formula~~Formula II:



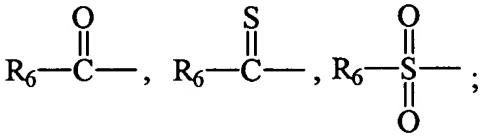
(II)

wherein

W represents a functional group which reacts with an active site residue of the targeted protease, ~~as for example,~~selected from -CN, -CH=NR_5,



R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-$lower alkyl, $-(CH_2)_m-O-$lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-$S-lower alkyl, $-(CH_2)_m-S-$lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, -(CH2)m-R7, -(CH2)n-OH, -(CH2)n-O-alkyl, -(CH2)n-O-alkenyl, -(CH2)n-O-alkynyl, -(CH2)n-O-(CH2)m-R7, -(CH2)n-SH, -(CH2)n-S-alkyl, -(CH2)n-S-alkenyl, -(CH2)n-S-alkynyl, -(CH2)n-S-(CH2)m-R7, $-C(O)C(O)NH_2$, or -C(O)C(O)OR'7;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-$alkyl, $-(CH_2)_m-O-$alkenyl, $-(CH_2)_m-O-$alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-$alkyl, $-(CH_2)_m-S-$alkenyl, $-(CH_2)_m-S-$alkynyl, or $-(CH_2)_m-S-(CH_2)_m-R_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{61} and R_{62}, independently, represent small hydrophobic groups;

Y_1 and Y_2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ~~(such as pinacol or the like),~~;

R_{50} represents O or S;

R_{51} represents N_3, SH_2, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure

X_1 represents a halogen;

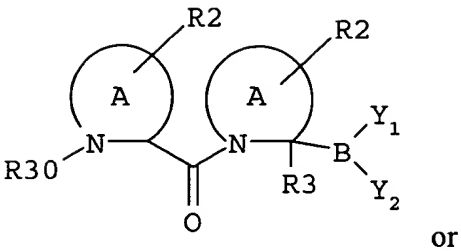
X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

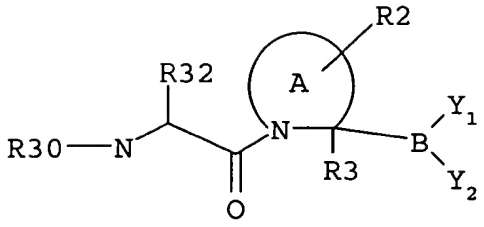
~~30~~29. (Amended) A method for modifiying, in an animal, metabolism of peptide hormone, comprising administering to the animal a composition including one or more boronyl peptidomimetic inhibitors of dipeptidylpeptidase IV (DPIV) in an amount sufficient to increase the plasma half-life of a peptide hormone, which peptide hormone is selected from ~~the group consisting of~~ glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

~~31~~30. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including boronyl peptidomimetic of a peptide selected from ~~the group consisting~~ Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

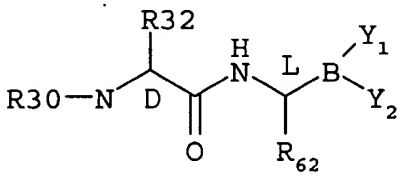
~~32~~31. (Amended) The method of claim 31, ~~wherien~~ wherein the boronyl peptidomimetic is represented in the general formula:



or



or



or

wherein

each A independently represents a 4-8 membered heterocycle including the N and ~~the~~ a Cα carbon;

R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-$lower alkyl, $-(CH_2)_m-O-$lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-$S-lower alkyl, $-(CH_2)_m-S-$lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

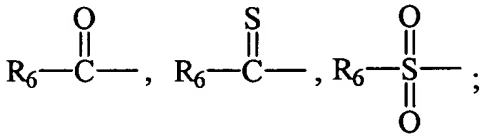
R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl ~~(such as a carboxyl, an ester, a formate, or a ketone)~~, a thiocarbonyl ~~(such as a thioester, a thioacetate, or a thioformate)~~, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-$lower alkyl, $-(CH_2)_m-O-$lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-$S-lower alkyl, $-(CH_2)_m-S-$lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, -(CH2)m-R7, -(CH2)n-OH, -(CH2)n-O-alkyl, -(CH2)n-O-alkenyl, -(CH2)n-O-alkynyl, -(CH2)n-O-(CH2)m-R7, -(CH2)n-SH, -(CH2)n-S-alkyl, -(CH2)n-S-alkenyl, -(CH2)n-S-alkynyl, -(CH2)n-S-(CH2)m-R7, -C(O)C(O)NH2, or -C(O)C(O)OR'7;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, or -$(CH_2)_m$-S-$(CH_2)_m$-R_7;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



;

R_{32} and R_{61}, independently, represent small hydrophobic groups~~, preferably lower alkyls, and more preferably methyl~~;

Y_1 and Y_2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, including cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ~~(such as pinacol or the like),~~ ;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

~~33~~32. (Amended) The method of claim ~~32~~31, wherein administering the boronyl peptidomimetic reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia.

~~34~~33. (Amended) The method of claim ~~32~~31, wherein the boronyl peptidomimetic has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

~~35~~34. (Amended) The method of claim ~~32~~31, wherein the boronyl peptidomimetic has an EC_{50} for inhibition of glucose tolerance in the nanomolar or less range.